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Intraoperative methadone: Rediscovery, reappraisal, and reinvigoration?

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Adequate relief of perioperative pain has been deemed a fundamental right of patients, and obligation of practitioners.¹ Inadequately relieved postoperative pain has numerous physiologic complications, attendant risk of increased morbidity, and causes needless suffering. More than 40% of postoperative patients report inadequate pain relief, or pain of moderate or greater intensity, despite treatment.¹⁻³ Unrelieved acute postoperative pain is a risk factor for the development of chronic postsurgical pain.^{4,5} It seems axiomatic that the duration of analgesia should match the duration of pain.

But how best to do so? The trend in anesthesia care over the past decades has been the use of opioids with successively faster elimination and successively shorter duration of effect (fentanyl, sufentanil, alfentanil, remifentanil). Use of short-duration intraoperative opioids, awakening patients in discomfort, and then attempting to play “catch-up” in the recovery room, often with the standard postoperative opioid morphine - the opioid with the longest (and long - 1 hr to peak effect) time to onset, appears to some to be suboptimal. The transition, from intraoperative anesthesia based on ultrashort opioids to postoperative analgesia, can be challenging - particularly for painful operations.⁶

Focusing on perioperative opioids, intravenous patient-controlled analgesia (PCA) has become the mainstay for providing postoperative pain relief over the past 2-3 decades. It is generally accepted that PCA provides better analgesia and patient satisfaction compared with conventional or nurse-administered opioids.^{3,5,7} However there is also awareness of the limitations of PCA. PCA is better suited to maintaining analgesia, after administration of appropriate opioid loading doses, than to achieving analgesia *de novo*. While PCA may be considered advantageous because it consumes less nursing time,³ the cost of pumps, disposables, and adverse events clearly also factors into assessing the overall cost-effectiveness of PCA. Adverse events may relate in part to pump programming errors, equipment malfunctions, PCA-by-proxy, and respiratory depression. The incidence of significant respiratory depression with PCA ranges from 0.1-1%, depending in part on the definition.⁸⁻¹¹ While this incidence has been variably referred to by some as low and by others as high, events can be catastrophic. It would seem axiomatic that decreasing postoperative opioid use, and the number of doses, would diminish the risk of untoward effects.

This issue of *Anesthesia & Analgesia* reports an investigation which reminds us of a longavailable, effective, and infrequently- (and perhaps under-) utilized alternative to the

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more conventional opioid paradigms described above.¹² That alternative is intraoperative methadone. For patients undergoing complex thoracolumbar spine surgery, Gottschalk *et al* provided total intravenous anesthesia with propofol (50-150 $\mu\text{g}/\text{kg}/\text{min}$ titrated to a target bispectral index) and either (by randomization) a sufentanil infusion (0.25 $\mu\text{g}/\text{kg}/\text{h}$ after a loading dose of 0.75 $\mu\text{g}/\text{kg}$) or a single bolus dose of methadone (0.2 mg/kg), both supplemented with 0.1 $\mu\text{g}/\text{kg}$ sufentanil for inadequate anesthesia. Postoperative analgesia was provided by PCA (fentanyl, morphine, or hydromorphone). Patients receiving methadone had significantly lower postoperative opioid requirements (median 98 vs 219 mg morphine equivalents 0- 72 hr postoperatively). Moreover, despite PCA, they also reported less postoperative pain. There was no difference in the incidence of side effects with methadone vs sufentanil. The authors conclude that a single intraoperative bolus of methadone improves postoperative pain control for patients undergoing complex spine surgery. Their results are unquestionably related to the slow rate of methadone elimination, and also attributed by the authors potentially to *N*-methyl-D-aspartate (NMDA) receptor antagonism by methadone.

Methadone is the opioid with the longest elimination half-life (Table 1). It is an efficacious and cost-effective analgesic for acute, chronic, neuropathic, and cancer pain, in adults, children and even neonates, and can be administered via oral, intravenous, and other parenteral routes.¹³⁻¹⁵ For cancer and neuropathic pain, it is an often-used alternative to morphine, and growing rapidly in first-line use.^{16,17} Nevertheless, it remains relatively invisible in the operating room and postoperatively.

The seminal investigations which introduced the use of methadone in the perioperative period were reported by Gourlay *et al*.¹⁸⁻²⁰ They studied orthopedic (typically anterior spinal fusion) and general surgery (typically open cholecystectomy) patients administered 20 mg methadone as an IV bolus following induction of anesthesia. Postoperatively, approximately one-third were entirely pain free and did not request any analgesics during the 72 hr postoperative observation period, approximately one-third used only oral non-opioid analgesics (aspirin, paracetamol), with a median duration of methadone analgesia (time to first oral analgesic request) of 26 hr, and only one-third of patients requested postoperative opioid analgesics, with a median duration of methadone analgesia (time to first opioid analgesic request) of 20 hr. Importantly, no patient had postoperative respiratory depression (rate < 10 breaths/min), and postoperative nausea/vomiting was not different than that conventionally encountered. In a follow-up investigation, with a greater percentage of (presumably more painful) upper abdominal incisions, after 20 mg intraoperative methadone, patients needed a median of two 5 mg methadone doses in the recovery room (which thereafter provided postoperative analgesia for 21 hr), and an additional 5 mg dose on the ward at that time, which often provided analgesia until hospital discharge.¹⁹ A third investigation was a double-blind comparison of perioperative methadone and morphine for upper abdominal surgery.²⁰ Patients received 20 mg opioid intraoperatively, and 5 mg doses in the recovery and surgical wards. In patients receiving methadone compared with morphine, the average time from initial pain control to first supplemental opioid dose in the surgical ward was significantly longer (21 vs 6 hr), and the average cumulative postoperative opioid use (12 vs 41 mg) and number of doses (2 vs 8) were smaller. Importantly, in these three investigations, there were no serious side effects, most notably respiratory depression, which is of particular concern with an opioid with prolonged effects. Together, this trio of investigations established methadone as providing excellent and prolonged intraoperative and postoperative analgesia, together with a fully acceptable safety profile.¹⁸⁻²⁰ Other investigations subsequently confirmed the effectiveness and utility of perioperative methadone, including the advantages of longer analgesia, fewer postoperative opioid doses, lower cumulative postoperative opioid use, and lower pain intensity compared

with morphine.²¹⁻²³ The investigation by Gottschalk *et al*, again reminds us of these pharmacologic advantages.¹²

Nevertheless, methadone is one of the most thoroughly studied yet persistently misunderstood drugs in medicine! There are several misperceptions.

One misperception is that the onset of methadone analgesia is slow, and therefore it is unsuitable for perioperative use. In fact, central nervous system effect site methadone concentrations rapidly equilibrate with plasma concentrations, evidenced by the short lag time between plasma concentrations and effects ($t_{1/2k_{e0}}$ of 4 min).²⁴ This is comparable to the rapid onset and effect compartment equilibration of fentanyl and sufentanil (5-6 min), which is exceeded only by that of remifentanyl and alfentanil ($t_{1/2k_{e0}}$ of 1 min for both). In contrast, there is a well-known lag time for the apparent central nervous system effect compartment penetration and onset time of morphine, where $t_{1/2k_{e0}}$ has been reported to exceed 4 hr^{25,26} Typical opioid $t_{1/2k_{e0}}$ values are compared in Table 1. The practical significance of these differences in central nervous system penetration is shown by comparing the time course of opioid plasma concentrations with the time course of effect, using miosis as a metric for the latter (Figure 1). Under similar conditions for all the opioids, the time course of miosis was quite similar to that of plasma concentrations, for alfentanil, fentanyl, and methadone. In contrast, for morphine, peak effects occurred hours after the peak of plasma concentrations. Onset of methadone analgesia is similarly rapid.²⁴ These considerations suggest that methadone is a rapid-onset drug, with an onset time similar to that of fentanyl and sufentanil. For a patient in pain, intraoperatively or postoperatively, needing an opioid where rapid analgesia is desired, methadone certainly appears preferable to morphine.

A second misperception is that the duration of methadone analgesia is shorter than its elimination half life (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142841.htm>).^{18,27,28} This is only partially true, and certainly not specific to methadone, because the relationship between elimination half-life and duration of effect depends also on the dose administered (for methadone, or any other opioid, or drugs in general). The clinical effect of small doses will be terminated by redistribution (where the elimination half-life is irrelevant), while the effect of larger doses (achieving biophase concentrations well in excess of the minimal effective concentration) will be terminated by systemic elimination (where the elimination half-life is relevant) (Figure 2). Thus, targeting doses and concentrations as high as possible above the minimal analgesic concentration, but below the threshold for respiratory depression, will achieve the longest-lasting analgesia. At concentrations approximately 20 mg, the duration of methadone analgesia approximates its elimination half life.

A third misperception attends to the metabolism of methadone, which inactivates the drug. Methadone is considered to have a highly variable clearance and significant susceptibility to metabolic drug interactions.²⁹ During the previous decade, its clinical metabolism and clearance have been attributed at various times to different cytochrome P450s (CYP), including CYP2D6, CYP2C19, and most consistently CYP3A4. Numerous studies, reviews, dosing guides, and the methadone label (approved by the FDA November 2007) warn about the potential for CYP3A4-mediated methadone drug interactions and the need to adjust dosing accordingly.³⁰⁻³³ Nevertheless, methadone metabolism may be less susceptible to inhibitory drug interactions that previously thought, and accumulated evidence demonstrates clearly that it is not a clinical CYP3A4 substrate and suggests instead that CYP2B6 is responsible for methadone metabolism and clearance.³⁴⁻³⁷

Based on these investigations, this author has used methadone as the primary intraoperative opioid for adult inpatients for over 25 yr. A single 20 mg intravenous bolus dose is administered before induction. This is reduced to 15 mg in patients “physiologically” older than 60 yr, because of declining methadone elimination and increased risk of respiratory depression with age.^{18,38} Other than occasional additional fentanyl (100–200 µg) use for induction/intubation, no other intraoperative opioids are administered. For postoperative analgesia, intravenous methadone (2–3 mg doses at >10 min intervals) is administered in the post-anesthesia care unit as needed, if a patient complains of pain and has an unstimulated respiratory rate greater than 10.²⁰

There are also unanswered questions about perioperative methadone use. There is little information available about the pharmacokinetics and pharmacodynamics of methadone in pediatrics.^{22,23,39} More information is needed about the effectiveness and safety in outpatients,⁴⁰ those who are opioid-tolerant, and, perhaps, the cost-effectiveness and safety of methadone compared with conventional PCA. Nevertheless, as reminded by Gottschalk, *et al*,¹² perhaps it is opportune to rediscover, reappraise, and reinvigorate the use of methadone in the perioperative period.

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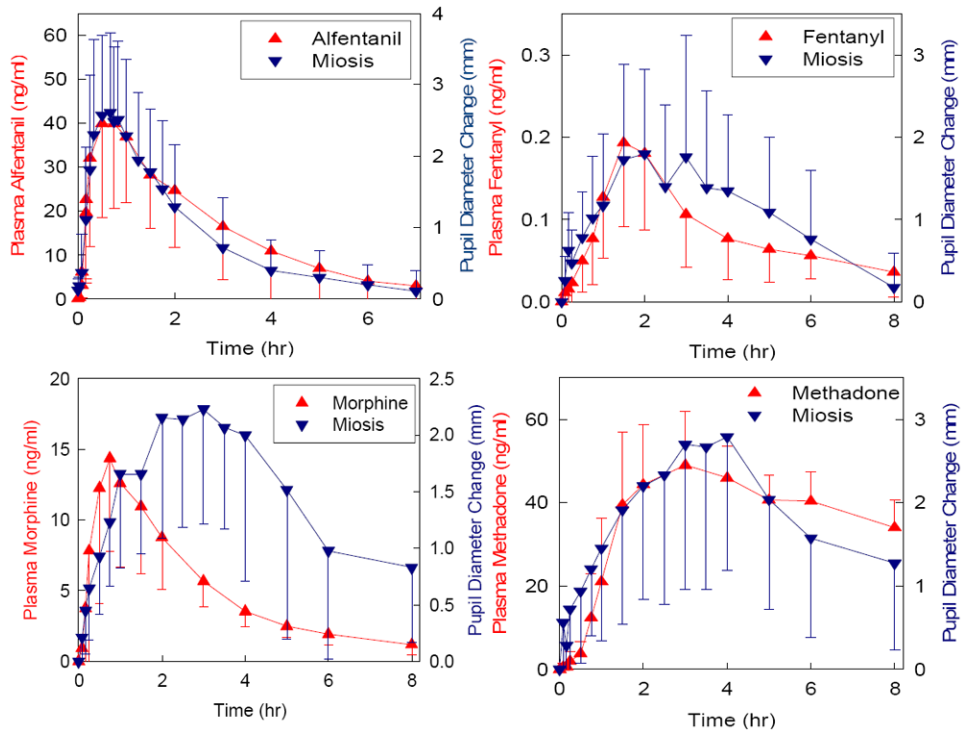


Figure 1. Relationship between opioid plasma concentration and onset of effect. Opioid effects was determined by pupil diameter change (miosis). Results are shown for alfentanil, fentanyl, methadone and morphine. Redrawn with permission.⁴¹⁻⁴⁴

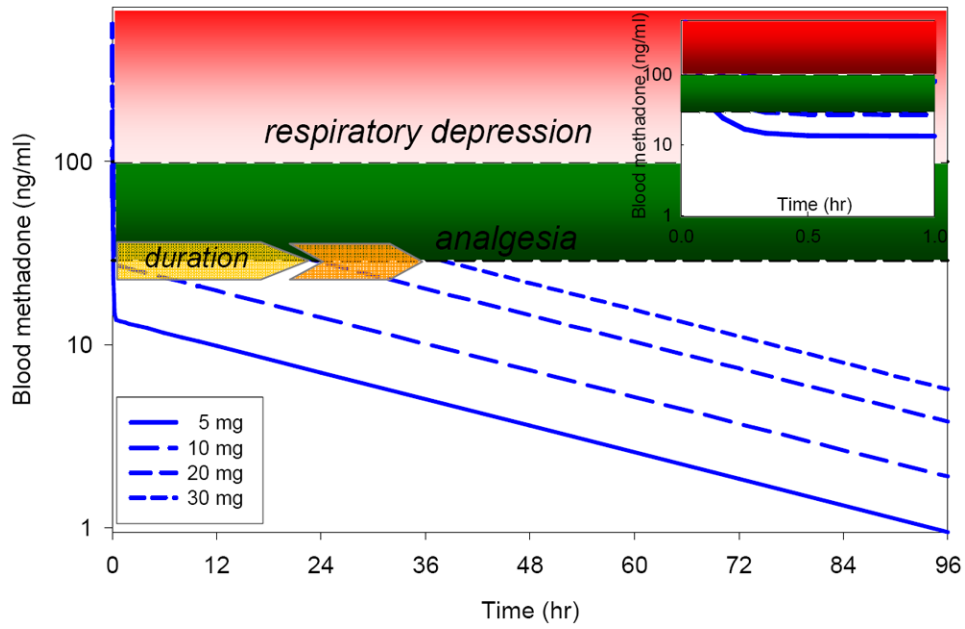


Figure 2.

Relationship between methadone dose and duration of effect. Simulated methadone blood concentrations vs time are based on the pharmacokinetic parameters of Gourlay et al,¹⁸ as are the minimal effective analgesic methadone concentration (approximately 30 ng/ml), and the threshold for significant (5-6 breaths/min) respiratory depression (approximately 100 ng/ml).¹⁹ Data are shown for intravenous bolus methadone doses of 5, 10, 20 and 30 mg. Estimated duration of analgesia for these doses is approximately <0.5, <0.5, 24 and 36 hr. Duration of analgesia is governed by redistribution (and the redistribution half-life of approximately 5 min) for the 5 and 10 mg doses, but by elimination (and the elimination half-life of approximately 30 hr) for the larger doses. The inset shows plasma concentrations for the first hr after dosing. Due to rapid redistribution, anticipated respiratory depression would be less than 30-45 min, even at the higher single bolus doses.

Table 1

Onset of effect and elimination of opioids

	$t_{1/2k_{e0}}$ *	Elimination $t_{1/2}$
remifentanyl	1 min	0.5 hr
alfentanil	1 min	1 hr
sufentanil	6 min	8 hr
fentanyl	5 min	8-10 hr
morphine	2-4 hr	2-3 hr
methadone	8 min	24-36 hr

* Based on published data.⁴⁵